REMARKS

The present invention relates to the use of bone marrow stromal cells to rescue a mammal from a lethal dose of total body irradiation. Claims 1-48 are pending and under consideration in the present application following entry of the present Amendment.

Applicants appreciate the time taken by the Examiners Kelly and Nguyen during the telephone interview that took place on May 9, 2004, with Applicants' representative, Kathryn Doyle (the undersigned). During the telephone interview, Applicants decided to amend the claims to identify the bone marrow stromal cells of the present invention to mean a cultured cell not modified in any way.

Claims 1, 5, 9, 13-16, 18-20, 22-24, 26-28 have been amended and claims 33-48 have been added herein. Claims 18-20, 22-24 and 26-28 have been amended to properly depend from claims 17, 21 and 25, respectively. Claims 33-48 have been added to indicate that the cells of the invention are cultured in vitro for approximately five weeks. Support for the amendments to the existing claims and the addition of new claims 33-48 is found in the as-filed specification as detailed below and, therefore, no new matter has been added by way of these amendments and additions.

Objection to the claims under 37 C.F.R. § 1.75 (Double Patenting)

The Examiner has objected to claims 18-20, 22, 24 and 26-28 under 37 C.F.R. § 1.75 as being a substantial duplicate (Double Patenting) of claims 2-4, 6, 8 and 10-12, respectively. Claims 18-20, 22-24 and 26-28 have been amended herein to depend from claims 17, 21 and 25, respectively. Specifically, claims 18-20, 22-24 and 26-28 as amended now depend from claims relating to culturing of the cells *in vitro* for no more than the third passage. As such, the objection to these claims under 37 C.F.R. § 1.75 as being a substantial duplicate (Double Patenting) of claims 2-4, 6, 8, and 10-12 is moot and should be withdrawn.

Rejection of claims 1-16, 18-20, 22, 24, and 26-28 under 35 U.S.C. § 112, first paragraph - written description

The Examiner has rejected claims 1-16, 18-20, 22, 24, and 26-28 under 35 U.S.C. § 112, first paragraph for lacking written description. Specifically, the Examiner asserts that the amendment to the claims to recite "primary cultured cells" by way of the Amendment dated

October 18, 2004, adds new matter because the specification does not specifically disclose a primary cultured cell. While not necessarily agreeing with the Examiner's reasoning, but rather in a good faith effort to expedite the prosecution of the present application, Applicants have replaced the phrase "primary cultured cells" with the phrase "not modified in any way." Support for this amendment is found in the specification as set forth below.

The recitation of the phrase "not modified in any way" is being made in view of the fact that the Examiner has indicated on page 4 of the Office Action dated January 3, 2005, that "it is unclear as to whether the primary cultured cells are primary because they are derived from an organism, whether they are able to increase hematopoiesis, whether they are not modified in any way (i.e. transformed), or whether because they are primary cultured cells as a result of the conditions of culturing." Accordingly, by way of the present Amendment, claims 1, 5, 9 and 13-16 have been amended to more particularly point out and distinctly claim the subject matter which Applicants and apparently the Examiner regard as the invention.

The as-filed specification amply supports the amendment to the claims with respect to the phrase "not modified in any way," and as such does not add new matter. Based upon the disclosure of the instant application, one skilled in the art would know that the cells of the present invention are not modified in any way (i.e. they have not been transformed by a virus, for example). This inference is exemplified by the fact that the Examiner himself states that the cells of the present invention are not modified in any way.

As set forth in MPEP §2163, "While there is no *in haec verba* requirement, newly added claim limitations must be supported in specification through express, implicit, or inherent disclosure." The as-filed specification describes a method of culturing a mixed population of bone marrow cells, containing both adherent and non-adherent cells, isolated from an allogeneic donor, wherein the population of adherent cells are separated from non-adherent cells. The adherent population of cells, which are referred to by the specification as bone marrow stromal cells, are cultured for a period of time prior to the administration to an irradiated mammal. Nowhere does the specification disclose that the bone marrow stromal cells of the present invention are modified. Certainly, the specification provides no teachings as to how to transform the cells of the present invention with a virus so as to render them immortalized as that term is known in the art. Based on the amendments made to claims 1, 5, 9, 13-16, Applicants

respectfully submit that the rejection of these claims under 35 U.S.C. § 112, first paragraph - written description, has been overcome and ask that the rejection be withdrawn.

Rejection of claims 1, 2, 4-6, 8-10 and 12-16 pursuant to 35 U.S.C. § 102(b)

The Examiner has maintained his rejection of claims 1-2, 4-6, 8-10 and 12-16 under 35 U.S.C. § 102(b) as being anticipated by Anklesaria et al. (1987, Proc. Natl. Acad. Sci., USA 84:7681-85). Specifically, the Examiner asserts that the teachings of Anklesaria anticipate the present invention because Anklesaria uses primary cells. Moreover, the Examiner contends that the claims would encompass the cells disclosed by Anklesaria because the claims do not exclude any particular conditions or steps. Applicants respectfully traverse this rejection for the following reasons.

The Examiner has also rejected claims 18, 20, 22, 24, 26 and 28 under 35 U.S.C. § 102(b) as being anticipated by Anklesaria et al. because claims 18, 20, 22, 24, 26 and 28 are apparently substantial duplicate of claims 1-2, 4-6, 8-10 and 12-16. However, claims 18, 20, 22, 24, 26 and 28 have been amended herein to properly depend from claims relating to having the cells be cultured *in vitro* for no more than the third passage, and therefore this rejection is rendered moot as to these claims.

As to the remaining rejected claims, claims 1-2, 4-6, 8-10 and 12-16, it is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Anklesaria must describe each and every element of claims 1-2, 4-6, 8-10 and 12-16 as amended herein, in order to anticipate these claims under 35 U.S.C. § 102(b), and this reference does not.

Anklesaria does not anticipate the present invention because the reference does not teach the cells of the present invention as encompassed by the amended claims and supported in the as-filed specification. Specifically, Anklesaria teaches a stable clonal cell line (GB1/6) which was established from the adherent layer of long-term marrow cultures from B6Cast mice. Anklesaria begins with a transformed/immortalized cell line (GB1/6), which is then selected for resistance to neomycin by culturing in the presence of G418. A subclone of these cells was then

isolated and administered to a mouse that had undergone total body irradiation to stimulate hematopoietic recovery in the mouse. Thus, this reference teaches that one skilled in the art can begin with a transformed/immortalized cell line, develop a subclone thereof, and administer the cells of the subclone to a mammal for the purpose of rescuing the mammal from total body irradiation.

Applicants instead use isolated bone marrow stromal cells that have not been modified in any way. The cells of the present invention are untransformed, particularly they are not virally transformed cells. The cells have been cultured for no more than the third passage, or the cells have been cultured for approximately five weeks. In any event, the cells of the present invention are cultured with minimal manipulation and are not modified by any viral infection thereof.

Each and every element of claims 1-2, 4-6, 8-10 and 12-16 is not found in Anklesaria, therefore this reference cannot anticipate the claims and the rejection of the same under 35 U.S.C. § 102(b) must be withdrawn.

Rejection of Claims 3, 7, 11, 19, 23 and 27 pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 3, 7, 11, 19, 23 and 27 pursuant to 35 U.S.C. § 103(a), as being obvious over Anklesaria et al., in view of Palsson et al. (U.S. Patent No. 5,635,386). Specifically, the Examiner contends that Palsson teaches the use of human hematopoietic stem cells and their cultures that "afford improved methods for bone marrow transplantation," and the combination of the teachings of Anklesaria with Palsson would arrive at the present invention. Applicants respectfully traverse this rejection for the following reasons.

As an initial matter, Anklesaria does not teach an isolated bone marrow stromal cell that has been cultured in a manner that does not modify the cell in any way. Rather, Anklesaria teaches a virally transformed cell. Further, the cells of the present invention include, but are not limited to cells that have been cultured for approximately five weeks and cells cultured for no more than the third passage. As such, one skilled in the art would recognize based on the teachings of the as-filed specification that the instant cells are short-term cultures per se. As such, the present invention offers an improvement and an unexpected result that short-term cultures according to the teaching of the specification can be used in lieu of long-term cultures per se or transformed cell lines to provide a therapeutic benefit in vivo.

Applicants submit that Anklesaria in view of Palsson cannot render claims 3, 7, 11, 19, 23 and 27 *prima facie* obvious under 35 U.S.C. §103(a). Palsson cannot cure the deficiencies of Anklesaria as discussed above and are not repeated here. Applicants contend that Palsson merely teaches hematopoietic stem cells.

More specifically, the MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

The first prong of the *In re Vaeck* test, the requirement that the references themselves or the knowledge in the art must provide some suggestion or motivation, has not been met in this instance. Applicants assert that Anklesaria offers no suggestion or motivation to modify the reference or to combine reference teachings to arrive at the present invention. Even if Anklesaria did in some way, which it does not, offer a suggestion or motivation to combine the references, Applicants contend that the combined teachings would teach away from the present invention. As discussed elsewhere herein, Anklesaria does not teach a short-term culture per se. Rather, Anklesaria teaches a virally transformed stable clonal cell line (GB1/6). As such, Anklesaria does not suggest Applicants' cells. Nowhere does Anklesaria offer a suggestion or motivation to use Applicants' cells for rescuing a mammal from total body irradiation.

The combination of Anklesaria with Palsson does not render the present invention obvious. The teachings of Palsson do not correct the deficiencies of Anklesaria. Similar to Anklesaria, Palsson does not teach Applicants' cell. Rather, Palsson teaches the use of human hematopoietic stem cells. For example, on page 11 of the present Office Action, the Examiner indicates that Palsson teaches "culturing human stem cells and/or human hematopoietic progenitor cells and/or human stromal cells in liquid culture." However, as indicated in column 10, Palsson teaches the culturing of stem cells throughout a culture period of at least five months. That is, Palsson teaches culturing stem cells for an extensive amount of time and passage number indicative of a long-term culture per se (see Example 1, column 33). Not only does Palsson not

teach the cells of the present invention, but Palsson does not even teach administering the cells to an irradiated mammal for the purpose of rescuing an animal from total body irradiation. Accordingly, Palsson, even in view of Anklesaria fails to offer a suggestion or motivation to modify the reference(s) to arrive at the instant invention.

The second criteria for establishing a *prima facie* case of obviousness is that there must be a reasonable expectation of success. Applicants contend that based on the disclosure set forth in Anklesaria, the skilled artisan would not have any reason to expect that Applicants' cell would rescue a mammal from a lethal dose of total body irradiation. Rather, upon reading Anklesaria, a skilled artisan would only have a reasonable expectation of success for using a transformed cell line to rescue a mammal from a lethal dose of total body irradiation. Therefore, Anklesaria fails to render the present invention *prima facie* obvious because Anklesaria offers no reason to suggest that Applicants' cell would successfully rescue a mammal from total body irradiation.

In addition, Palsson, when combined with the teachings of Anklesaria does not generate a reasonable expectation of success in rescuing a mammal from total body irradiation by administering Applicants' cell to the mammal. Palsson at best teaches long-term cultured stem cells. One skilled in the art would have no reasonable expectation of success in combining the teaching of the two references to arrive at the present invention, wherein the cells are cultured with minimal manipulation prior to the administration to the mammal in need thereof. The combination of the references does not provide a reasonable expectation of success using the cells of the present invention for rescuing a mammal from total body irradiation.

The third prong in establishing a *prima facie* case of obviousness requires the prior art reference or references to teach or suggest all of the claim limitations. As discussed elsewhere herein, Anklesaria does not teach the cells of the present invention as encompassed by the claims and defined by the specification. Therefore, Anklesaria does not teach or suggest all embodiments of the claims. In addition, the teachings of Palsson, as discussed elsewhere herein are unable to correct the deficiencies of Anklesaria, and therefore, Anklesaria in view of Palsson, cannot render the present invention *prima facie* obvious. Rather, the combination of these references would teach away from the present invention because both Anklesaria and Palsson teach using a different cell than Applicant's cell. Accordingly, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-48 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

By: _____

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Enclosures: Petition for Extension of Time